

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF ANDREAS WERNER
SUPERSAXO ET AL
SERIAL NO.: 09/306,006
FILED: JUNE 5, 1999
FOR: USE OF NANODISPERSIONS IN PHARMA-
CEUTICAL END FORMULATIONS

Group Art Unit: 1617

Examiner: S. SHARAREH

DECLARATION UNDER RULE 132

I, Andreas Werner Supersaxo, a citizen of the Swiss Confederation, residing in Baar, Switzerland, hereby declare:

1. That I am a co-inventor of the invention disclosed and claimed in the above identified patent application;
2. That I have been employed by Vesifact AG since January 1, 1998, specializing in research of nano-sized carrier systems for life science products;
3. That I am presently head of R & D, and have held this position since January 1, 1998;
4. That I am engaged in the research and development of nano-sized carrier systems for life science products;
5. That I consider myself an Expert in preparation of drug delivery systems, especially lipid based delivery systems such as liposomes, mixed micelles and microemulsions;
6. That prior to my employment at Vesifact AG, I was an employee of F.Hoffmann-La Roche AG Basel, Switzerland and of Syntex Research, Palo Alto, California, USA;
7. That I received my Ph. D. in pharmaceutics in 1986 at the Swiss Federal Institute of Technology, Department of Physical Pharmacy, Zurich, Switzerland;
8. That I am a named inventor in U.S. Patents Nos.: 5,376,646; 5,470,582; 5,759,827 and 6,030,602, and
9. That I carried out the following preparative Examples (1) – (3).

It has been the object of the tests reported below to compare a nanodispersion containing a coemulsifier according to the invention with a nanodispersion of the same components but containing a polyethoxylated sorbitan fatty acid ester as coemulsifier, which component has been recommended in WO 96/37192.

I. Comparative Test

The following dispersions were made according to the method described in Example 2 of WO 96/37192:

Nanodispersion 1 (Prior Art; Example 2 of WO 96/37192)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
TWEEN 80 (HLB: 15)	3.35
10 mM Phosphate buffer pH 6.0	90.00

Nanodispersion 2 (Invention)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
SOLUTOL HS 15 (HLB: 14-16)	3.35
10 mM Phosphate buffer pH 6.0	90.00

Nanodispersion 3 (Invention)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
CREMOPHOR EL (HLB: 12-14)	3.35
10 mM Phosphatpuffer pH 6.0	90.00

For the assessment of storage stability, the dispersions were filled into 20 ml glass vials and stored for a period of 12 months at 40°C under sterile conditions. The following table shows results of visual assessments before and after storage.

Table: Appearance of formulations before and after storage (12 months, 40°C)

No.	Coemulsifier (INCI name)	Coemulsifier (chemical name)	Appearance before storage	Appearance after storage
1	TWEEN 80 (Polysorbate 80)	Polyethoxylated sorbitan fatty acid ester	opalescent, transparent	strongly opalescent to milky
2	SOLUTOL HS 15 (PEG-15 Hydroxystearate)	Polyethoxylated fatty acid	opalescent, transparent	opalescent, transparent
3	CREMOPHOR EL (PEG-35 Castor Oil)	Polyethoxylated triglyceride	opalescent, transparent	opalescent, transparent

II. Discussion of Test Results

The prior art dispersion containing a polyethoxylated sorbitan fatty acid ester as coemulsifier has strongly changed its visual appearance after 12 months storage at 40°C. Corresponding dispersions of the invention are visually unchanged after the same storage conditions.

III. Conclusion

The results presented above show that the replacement of the polyethoxylated sorbitan fatty acid ester by an alternative polyethoxylated coemulsifier as of present invention leads to a distinctly improved storage stability of the formulation.

These results are important because maintenance of the formulation's physical appearance during storage is one of the key factors for market acceptance.

These results are surprising because prior art contains no hint that replacement of polyethoxylated sorbitan fatty acid esters by an alternative polyethoxylated coemulsifier as of present invention might provide any advantage.

Hence, the results supply evidence that the subject matter claimed in present application is non-obvious in the light of prior art.

I, Andreas Werner Supersaxo, further declare that all statements made herein of personal knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 4th day of October 2005

Andreas Werner Supersaxo

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